

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 4

**REMARKS**

Claims 1-8 are pending. Claims 3-5 have been canceled. Claims 1, 2, and 6 have been amended to more particularly point out what applicants regard as the invention. Support for these amendments is found in the specification, for example, at page 15, lines 2-5; page 33, line 13; page 36, lines 27-31; and page 38, lines 24-30. Thus, claims 1, 2, and 6-8 will be pending and under examination upon entry of this Amendment.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the April 28, 2004 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

**Formalities**

The Examiner noted that the references listed in the specification do not comprise a proper information disclosure statement as required by 37 C.F.R. §1.98(b).

In response, applicants note that an Information Disclosure Statement in accordance with 37 C.F.R. §1.98 was filed along with the instant application on January 27, 2000, including a PTO-1449 form and Exhibits 1-5. Applicants respectfully request that the references listed in the Information Disclosure Statement be made of record, and that a copy of the initialed PTO 1449 form be returned to applicants.

**Rejections Under 35 U.S.C. §103(a)**

The Examiner rejected claims 1-5, 7, and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Shuman (1992) in view of Bjornson et al. (1994), as evidenced by Stern et al. and Karn et al.

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 5

In response to the rejection of claims 3-5, applicants note that these claims have been canceled, rendering the rejection moot.

In response to the rejection of claims 1, 7, and 8, applicants respectfully traverse. Applicants maintain that the cited references fail to support a *prima facie* case of obviousness for the reasons of record and for the additional reasons set forth below.

The Examiner has failed to establish a *prima facie* case of obviousness because the method of Shuman, combined with the teachings of Bjornson, Stern, and Karn, fails to teach each and every aspect of the claimed invention.

The rejected claims provide a method for detecting the release of a single-stranded RNA from an RNA duplex which comprises the steps of (a) admixing an RNA helicase with the RNA duplex under conditions permitting the RNA helicase to unwind the RNA duplex and release single-stranded RNA therefrom, wherein the RNA duplex is (i) present in an amount within the nanomolar range and (ii) comprises a first RNA having a first fluorescent label attached at its 5' end and a second RNA having a second label attached at its 3' end, wherein the first fluorescent label produces a luminescent energy pattern when the first RNA is present in the duplex, which differs from the luminescent energy pattern the first RNA produces when it is not present in the RNA duplex; and (b) detecting a change in the luminescent energy pattern produced by the first label so as to thereby detect release of single-stranded RNA from the RNA duplex.

None of the cited references teaches the detection of nanomolar amounts of fluorescently labeled RNA, nor do any of

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 6

the cited references teach a duplex RNA having a different label at the 5' and 3' end of each antiparallel strand in the duplex.

Shuman teaches a method for detecting RNA helicase activity utilizing *radiolabeled* duplex RNA. Shuman fails to teach fluorescently labeled RNA.

Bjornson teaches a method for detecting DNA helicase activity utilizing fluorescently labeled duplex DNA. Bjornson fails to teach fluorescently labeled RNA.

Stern describes in general terms a method utilizing fluorescently labeled RNA. Stern fails to teach the detection of nanomolar amounts of fluorescently labeled RNA. See e.g., columns 14 and 15, and Figure 5 of Stern.

Karn describes in general terms the fluorescent labeling of an RNA on its 5' or 3' end. Karn does not teach a duplex RNA. Karn also fails to teach the detection of nanomolar amounts of fluorescently labeled RNA. Instead, Karn uses nanomolar amounts of labeled RNA to quench the fluorescent signal of a labeled antimicrobial compound. Thus, the labeled RNA is not detected in the method of Karn. Instead, the fluorescence of the labeled antimicrobial compound, and specifically the quenching of that fluorescence, is detected in the method of Karn. See e.g., columns 20-24, and Figures 6-9.

In summary, applicants maintain that the Examiner has failed to demonstrate a *prima facie* case of obviousness because the cited references in combination fail to teach the elements of the instant methods detecting nanomolar amounts of fluorescently labeled RNA. Given this deficiency, the cited references cannot be combined to produce the instant methods,

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 7

nor can they provide any reasonable expectation of success in making that combination.

The Examiner also rejected claim 6 under 35 U.S.C. §103(a) as allegedly unpatentable over Shuman (1992) in view of Bjornson et al. (1994) and further in view of Nazarenko et al. (1999).

In response, applicants respectfully traverse for the reasons of record and for the following additional reasons.

Claim 6 depends from claim 1 and further provides that the first label is fluorescein isothiocyanate and the second label is rhodamine isothiocyanate.

According to the Examiner, Nazarenko teaches an extensive list of suitable moieties that can be used as donor or acceptor molecules for fluorescence resonance energy transfer ("FRET") reactions, including the fluorescein and rhodamine labels recited in claim 6. However, Nazarenko does nothing to overcome the deficiencies of Shuman or Bjornson in failing to teach the detection of nanomolar amounts of fluorescently labeled RNA. Therefore, Nazarenko, combined with Shuman and Bjornson, fail to render obvious the claimed method.

The Examiner also rejected claims 1-3, 7, and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Eggleston (1996).

In response to the rejection of claim 3, applicants note that claim 3 has been canceled, rendering the rejection moot.

In response to the rejection of claims 1, 2, 7, and 8, applicants respectfully traverse.

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 8

Eggleston teaches a helicase assay based upon dye displacement detection methods in which fluorescent dyes which bind to double-stranded DNA are displaced as the DNA is unwound. Eggleston fails to teach end-labeled DNA or RNA. Applicants note that the instant claims do not provide DNA methods or dye displacement assays of the type taught by Eggleston. Accordingly, Eggleston is inapposite to the instant claims, and thus fails to render them obvious under 5 U.S.C. §103(a).

The Examiner also rejected claims 1-3, 7, and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Kowalczykowski et al. (1998).

In response to the rejection of claim 3, applicants note that claim 3 has been canceled, rendering the rejection moot.

In response to the rejection of claims 1, 2, 7, and 8, applicants respectfully traverse.

Applicants maintain that Kowalczykowski fails to render obvious the claimed methods for the same reasons as Eggleston fails to do so, namely because the dye displacement assay taught by Kowalczykowski is inapposite to a determination of obviousness with respect to the instant claims which do not provide such a method.

The Examiner also rejected claims 4 and 5 under 35 U.S.C. §103(a) as allegedly unpatentable over Eggleston or Kowalczykowski as applied to claims 1-3, 7, and 8, above in view of Bjornson et al. and as evidenced by Stern et al. and Karn et al.

In response to the rejection of claims 4 and 5, applicants note that these claims have been canceled, rendering the rejection moot.

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492, 954

Filed: January 27, 2000

Page 9

Finally, the Examiner rejected claim 6 under 35 U.S.C. §103(a) as allegedly unpatentable over Eggleston or Kowalczykowski as applied to claims 1-3, 7, and 8, above in view of Bjornson et al. and as evidenced by Stern et al. and Karn et al.

In response, applicants respectfully traverse. The Examiner alleged that it would have been *prima facie* obvious to have substituted the labels fluorescein and rhodamine in the method of either Eggleston or Kowalczykowski in view of Bjornson. Applicants respectfully disagree.

The methods of Eggleston and Kowalczykowski rely upon the ability of certain dyes ("markers") to differentially bind to double-stranded DNA versus single-stranded DNA. (See e.g., column 3 of Kowalczykowski, which states that the marker must provide greater luminescent intensity in the presence of double-stranded nucleic acid than in the presence of a molar-equivalence of single-stranded nucleic acid). Thus, the dye displacement methods of Eggleston and Kowalczykowski are entirely different from the FRET-based methods of the instant invention. Accordingly, Eggleston and Kowalczykowski are inapposite to the determination of whether the claimed methods are obvious under 35 U.S.C. §103(a). Moreover, neither Eggleston nor Kowalczykowski overcome the deficiencies of Bjornson, Stern, and Karn, in failing to teach the detection of nanomolar amounts of fluorescently labeled RNA, wherein the RNA is labeled at its 3' or 5' end.

In summary, applicants maintain that the Examiner has failed to demonstrate a case of *prima facie* obvious with respect to the claims pending in this application, and applicants respectfully request that this rejection be withdrawn.

Applicants: Anna Marie Pyle and Eckhard Jankowsky  
Serial No.: 09/492,954  
Filed: January 27, 2000  
Page 10

**Provisional Double Patenting Rejection**

The Examiner provisionally rejected claims 1-8 under 35 U.S.C. §101 as allegedly claiming the same subject matter as claims 1-8 of copending application U.S. Serial No. 10/182,362. The Examiner stated that the claims appear to be identical in scope.

In response to the Examiner's provisional rejection, but without conceding the correctness thereof, applicants will consider canceling claims 1-8 of copending application U.S. Serial No. 10/182,362 when the instant claims are otherwise deemed allowable.

**Summary**

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Applicants: Anna Marie Pyle and Eckhard Jankowsky

Serial No.: 09/492,954

Filed: January 27, 2000

Page 11

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Respectfully submitted,

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